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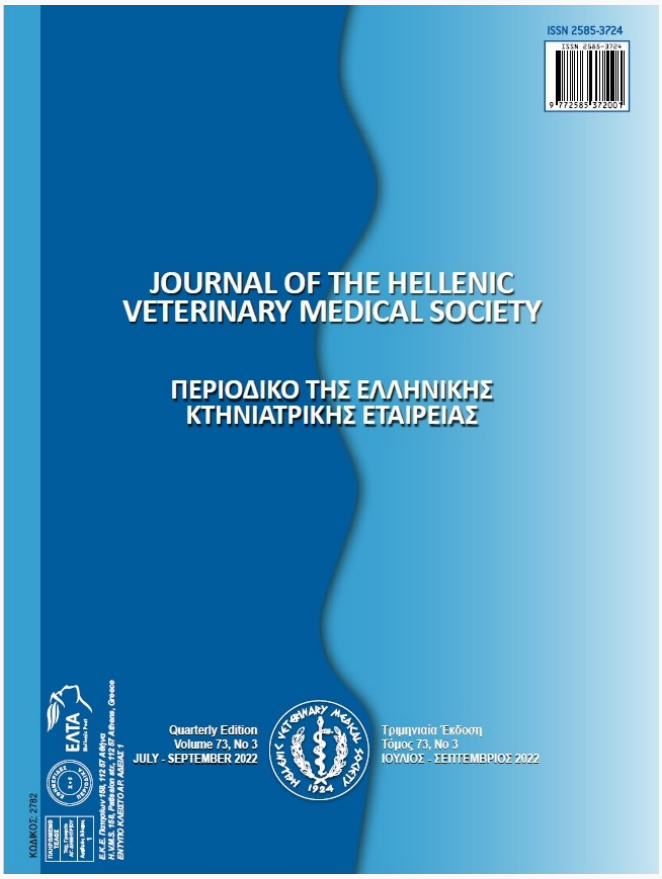

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Case report
Κλινικό περιστατικό

Mast Cell Tumour and Mammary Gland Carcinoma Collision Tumour in a dog. Case report and literature review.

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ABSTRACT: Collision tumours are the coexistence, at the same site, of distinct tumours not macroscopically distinguishable and consisting of two independent cell populations without histological admixture. In human medicine, collision tumours in different anatomical sites have been described. In the veterinary literature, few cases exist so far. A 12-year-old female Labrador with a mammary gland single nodular lesion was presented for clinical examination. The nodule was surgically removed and underwent histological and immunohistochemical analysis. Histopathological examination revealed two distinct malignant tumours: a mammary gland carcinoma and a cutaneous mast cells tumour. To the author's knowledge, the paper reports the first case of a collision tumour composed of mammary gland neoplasia and mast cell tumour. The rising interest in collision tumours suggests widening their knowledge and setting up a multimodal approach that includes surgery and targeted therapy.

Keywords: Collision tumour, dog, mammary gland cancer, mast cell tumour

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CASE HISTORY

Neoplasms developing at the same site do not fit any cancer classification because of their distinct morphological characteristics. In 2009, Satter attempted a classification into four categories: combined tumours consisting of two populations of malignant and phenotypically different cells which are intertwined; biphenotypic tumours, developing from a common stem cell precursor that differentiates into two phenotypically similar populations of cancer; colonization, usually referred to neoplastic melanocytic cells that infiltrate a basal cell carcinoma; collision tumours (CTs) formed by two independent neoplasms, each originating from different tissues (Satter et al., 2009). CTs, at the clinical and macroscopical examination, resemble a single tumour. Histological and immunohistochemical analysis reveals two phenotypically distinct cell populations that maintain sharp, distinct boundaries and can be composed of two benign tumours, a benign and a malignant tumour, or two malignant tumours (Bulte et al., 2020; Mancebo et al., 2015; Pallatto & Bechtold, 2018; Rodríguez et al., 2016; Scott et al., 2017).

In human medicine, some anatomical sites seem to be more involved than others, such as the mammary gland (Alawami et al., 2021), the genital tract (Tan et al., 2021), the urinary tract (Lamprou et al., 2021), the gastrointestinal tract (Yuan et al., 2021); the larynx and thyroid (Coca-Pelaz et al., 2016), the skin and appendages (Mancebo et al., 2015; Mizuta et al., 2021; Satter et al., 2009). Moreover, carcinomas and lymphohematopoietic system neoplasms or melanoma or sarcomas are frequently associated (Jafarian et al., 2015; Mancebo et al., 2015; Yuan et al., 2021).

In veterinary medicine, the literature on CTs is limited to very few case reports. In dogs have been described collisions of gingival squamous cell carcinoma and melanoma (Rodríguez et al., 2016); cutaneous melanoma and anaplastic sarcoma in the upper lip (Jakab & Balka, 2012); canine hepatoid gland carcinoma and perianal hemangiosarcoma (Andras et al., 2010,); a case of mast cell tumour and fibrosarcoma in the skin (Scott et al., 2017); mast cell and plasma cell collision tumour in the spleen (Pallatto & Bechtold, 2018) and a case of collision tumour of two nodal metastases of apocrine gland adenocarcinoma and vulvar mast cell tumour (Gibson et al., 2020). Veterinary literature reports are resumed in Table 1. In this case, we describe the pathological findings of a collision tumour detected in a canine mammary gland.

A 12-year-old, entire female Labrador was presented for a neoformation located close to the nipple in the left thoracic mammary gland (T2). (Figure 1). The nodule appeared round-shaped, with regular margins, sized less than 3 cm, movable and covered by ulcerated skin. (Figure 1). The blood count, biochemical examination, chest X-ray, and abdominal ultrasound tests were negative. After a preliminary cytological diagnosis, the patient underwent surgery, histological analysis, and tumour staging. The nodule was surgically removed and sent to the Unit of Pathology, Department of Veterinary Sciences, University of Messina (Italy) for gross and histological examination.

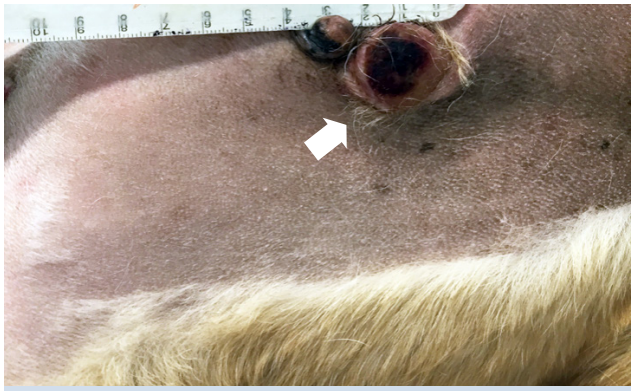

Figure 1. Neoformation on the left pair of thoracic mammary glands; the lesion was located close to the nipple, appeared as a single, round-shaped nodule, with regular margins, sized less than 3 cm, movable, and was covered by ulcerated skin (white arrow)

Table 1: Collision tumours described in veterinary literature (source Pubmed and Scopus)

Breed	Localisation	Collision Tumour		Bibliography
		Tumour 1	Tumour 2	
Cocker spaniel	Oral cavity	Squamous carcinoma	Malignant Melanoma	Rodriguez et al., 2016
Tibetan spaniel	Oral cavity	Anaplastic sarcoma	Melanoma	Jakab and Balka, 2012
Labrador Retriever	Perianal region	Hepatoid gland carcinoma	Hemangiosarcoma	Scott et al., 2017
English Mastiff	Spleen	Mast cell tumour	Plasma cell tumour	Pallatto and Bechtold, 2018
Labrador Retriever	Iliac metastatic lymph node	Adenocarcinoma	Mast cell tumour	Gibson et al., 2020
Golden Retriever	skin	Fibrosarcoma	Mast cell tumour	Scott et al., 2017

Tissues were fixed in 10% buffered formalin and paraffin wax embedded; 4 μm thick sections were stained for histochemical stains (Hematoxylin and Eosin (HE), Toluidine Blue). For immunohistochemistry, the labelled avidin-biotin (LAB) method was used. In detail, slides were steamed in 0.01 mol/L sodium citrate buffer (pH 6) in a microwave oven. Endogenous peroxidase activity was quenched by 0.3% hydrogen peroxide in methanol, while non-specific protein binding of were blocked by incubation with 2.5% bovine serum albumin (BSA). Sections were labelled with the primary antibodies (Abs), anti- Pan-cytokeratin/AE1-AE3 (mouse monoclonal, dilution 1:200, Santa Cruz Biotechnology), and c-Kit/C19 (rabbit polyclonal, dilution 1:100-1:200, Santa Cruz Biotechnology), followed by incubation overnight at 4 °C. Slides were then incubated at room temperature for 30 minutes with biotinylated secondary antibodies (goat anti-rabbit biotinylated IgG, dilution 1:200, Biospa; goat anti-mouse biotinylated IgG, dilution 1:200, Biospa), and by an avidin peroxidase complex (Biospa, Milan, Italy). The reaction was developed with the DAB peroxidase (HRP) substrate kit, 3,30-diaminobenzidine (Vector Laboratories, Burlingame, CA, USA), and counterstained with haematoxylin. Negative controls were also performed by omission of primary Abs, the substitution of primary Abs with normal IgGs, and substitution of primary Abs with non-reactive antibodies of the same species and immunoglobulin class. The immunohistochemical stain was interpreted by assessing the intensity of labelling. Cytoplasmic and/or membrane immunoreactivity was considered positive.

Histological examination revealed two neoplastic lesions separated by vascularized stromal tissue. The main component consisted of a well-demarcated dermal area made of densely packed neoplastic mast cells beside an area of the mammary gland. The mammary gland tissue was affected by epithelial lesions of increasing severity from hyperplasia/dysplasia to tubular carcinoma according to the most recent classification (Zappulli et al., 2019). The mammary gland tubular carcinoma was assigned to grade 1 according to Peña et al. (2013). The neoplastic mast cells were in groups or cords separated by thin fibrovascular or thick fibro collagenous stroma with areas of hyalinization. The cells showed moderate pleomorphism and distinct cytoplasm holding fine, intracytoplasmic granules. In some of them, the cytoplasm was indistinct, and the granules were large and hyperchromatic or absent. Nuclei were round to indented with scattered chromatin and single nucleoli, and mitotic index ≤ 5 mitoses over ten fields. Using the Patnaik/Kiupel grading systems together resulted in a mast cell tumour grade II/low grade (Kiupel et al., 2011; Patnaik et al., 1984).

The immunostaining for c-Kit showed a focal or diffuse cytoplasmic staining of mast cells in the solid lesion. According to Kiupel et al. classification (Kiupel et al.,2004) the mast cell tumour showed a KIT-II pattern. Moreover, positivity for c-Kit was detectable even in the mammary gland epithelium both in hyperplastic and cancerous areas (figure 2).

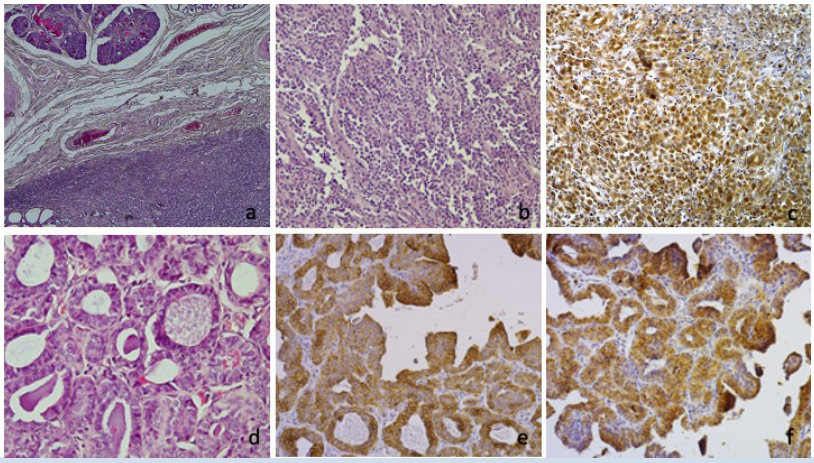

Figure 2. Collision Tumour in the mammary gland. (a) Two neoplastic lesions separated by vascularized stromal tissue (H&E, 5X); (b) well-demarcated area of densely packed neoplastic mast cells in groups or cords separated by fibro collagenous stroma with areas of hyalinization (H&E, 20X); (c) cytoplasmic expression for c-Kit, focal or diffuse, in the neoplastic mast cells (IHC, DAB, 20x); (d) epithelial lesions of increasing severity varying from hyperplasia/dysplasia to tubular carcinoma of the mammary gland (H&E, 10X); (e) positive labelling of neoplastic epithelial cells for cytokeratins AE1/AE3 (IHC, DAB, 20x); (f) moderate or mild cytoplasmic expression for c-Kit in the neoplastic mammary gland (IHC, DAB, 20x)

DISCUSSION

This report describes the clinical-pathological findings in a dog with a mammary gland collision tumour composed of a tubular mammary carcinoma and mast cell tumour.

A collision tumour consists of two neoplastic populations, each originating from different tissues, that grow separately but in the same anatomical area and appear macroscopically as a single lesion without distinctive clinical features. Various etiopathogenetic hypotheses explain the developing mechanisms of CTs. Random development in the same venue of two different primary tumours; simultaneous development under the influence of the same carcinogenic factor (i.e., radiation) of two morphologically distinct neoplasms; alteration or interaction of the microenvironment induced by the presence of a primary tumour which produces epidermal or stromal changes that allow the development of a second independent neoplasm through paracrine effects (Bulte et al., 2020; Mancebo et al., 2015; Scott et al., 2017).

In human medicine, the most observed tumour association is between breast cancer and chronic lymphocytic leukaemia (CLL) and/or lymphoma (Dialani et al., 2013; Jafarian et al., 2015). These two associations have also been described in other organs, such as the cervix, thyroid, colon, and skin. Among the various pathogenetic hypotheses, some authors have suggested that this phenomenon could result from a recruiting of immune pools in patients (Catteau et al., 2011).

In the case herein described the dog mammary gland cancer was associated with a neoplasm of cells of myeloid origin. The mast cell tumour could have progressed from the initial colonization of mast cells enrolled by the presence of mammary neoplasia.

Mast cells accumulate in the stroma at the periphery of cancers, exerting protumoural or antitumoural effects by the mean of mechanisms still unknown both in human and veterinary medicine (Ribatti, 2013; Sfacteria et al., 2021). Their presence and the variety of mediators released help to reshape the microenvironment and thus the behaviour of the tumour (Aponte-López et al., 2018). Therefore, in the case here described, cannot be excluded that alterations of the microenvironment due to the presence of breast cancer, could deviate the normal maturation process of mast cells, promoting carcinogenesis and neoplastic proliferation, possibly through mutations of the c-Kit receptor (Kiupel et al., 2004; Kwok et al., 2012). On the contrary, it could be feasible that the presence of a mast cell tumour could have altered the normal microenvironment leading to the onset of breast cancer, being the mammary gland epithelium positive for c-Kit (Morini et al., 2004).

Normal and hyperplastic mammary tissues show a moderate to strong diffusely cytoplasmic and membranous c-Kit positivity even though the relationship between the tumour histotype and the presence or absence of -c-Kit expression is still debated. Recently published studies have demonstrated a decrease in c-KIT expression in benign tumours as well as in the tubulopapillary carcinoma; no c-KIT expression is reported in high-grade carcinoma, although a cytoplasmic expression pattern could partially increase cellular proliferation (Brunetti et al., 2014; Gattino et al., 2018; Morini et al., 2004).

This case report aims to add an extra contribution to the Veterinary Medicine literature on collision tumours. According to the authors' knowledge, this is the first case of tubular mammary gland cancer along with a mast cell tumour. Moreover, the mammary region has never been reported as the location of CTs so far. The occurrence of these neoplastic entities underlines the need for a strict collaboration between the clinician and pathologist to promptly diagnose these lesions and prevent complications or metastasis due to the presence of a second tumour. The rising interest in collision tumours suggests widening their knowledge and setting up a multimodal approach that includes surgery and targeted therapy.

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ANIMAL WELFARE: all methods and procedures used in this study followed the guidelines of the Italian law (D.L. 04/3/2014 n. 26) and EU directive (2010/63/EU) on the protection of animals used for scientific purposes. This study did not require approval from authorities or the organization's ethics committees.

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